UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: 28 June 2016

SUBJECT: **Penflufen.** Human Health Risk Assessment to Support New Uses on Bulb Vegetables (Crop Group 3-07) and Sugar Beets.

PC Code: 100249
Decision No.: 507163, 507796
Petition Nos.: 5E8382, 5F8379
Risk Assessment Type: Single Chemical, Aggregate

DP Barcode: D428981, D429566
Registration No.: 264-1118, 264-1119, 264-1122
Regulatory Action: Section 3 Registration
Case No.: NA

TXR No.: 0053477
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CAS No.: 494793-67-8
40 CFR: § 180.664

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1.0 Executive Summary

Penflufen (N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1H-pyrazole-4carboxamide) is a carboxamide fungicide proposed for use primarily as a seed treatment for protection against certain soilborne, seedborne, and post-emergent diseases of crops. Penflufen's pesticidal mode of action is as a mitochondrial inhibitor, registered for use on a variety of agricultural crops. The exposure pathways expected for penflufen are dietary exposure via food and drinking water, and occupational exposures from seed treatment use on the proposed uses via the inhalation route. There are no registered or proposed residential uses, and residential exposure is not expected from the commercial use of this product. The Agency has received petitions from Bayer CropScience and from the Interregional Project Number 4 (IR-4) to register a flowable suspension concentrate (FS) formulation of penflufen on sugar beets and Crop Group 3-07 (bulb vegetables). Penflufen is being reviewed as part of a work-sharing project with Canada's Pesticide Management Regulatory Authority (PMRA).

No new toxicology data have been submitted for penflufen in support of the registered/proposed uses. For this assessment, the toxicological endpoints, points of departure (PODs), and uncertainty factors selected for risk assessment remain the same as in the previous assessment.

The toxicology database for penflufen is complete. Although an inhalation toxicity study is not available, based on weight of evidence considerations, the Hazard Science Policy Council (HASPOC) concluded that an inhalation study is not needed. The HASPOC also concluded that a comparative thyroid study is not needed for penflufen at this time due to the limited use pattern and low exposure and risk estimates associated with the current and proposed uses. The need for the study will be revisited in light of any changes to the use pattern or risk estimates.

The liver and thyroid are targets for penflufen and effects are observed throughout the toxicological database. There is no concern for increased susceptibility in developmental toxicity studies; qualitative susceptibility was seen in the rat reproduction study. Decreased motor and locomotor activity were observed in rats after acute and subchronic oral exposure in neurotoxicity studies; neuropathological lesions were not observed in either study. The effects observed in the penflufen toxicology database are well characterized, and there are clear NOAELs for the effects seen. Penflufen is classified as having "suggestive evidence of carcinogenicity," based on limited evidence of carcinogenicity (histiocytic sarcomas) in male rats. There is no mutagenicity concern for penflufen.

For acute dietary exposure and risk assessment, the point of departure (POD) and endpoint were selected from the rat neurotoxicity study based on effects seen in females (i.e. decreased motor and locomotor activity). Chronic dietary exposure and risk assessment, the point of departure (POD) and endpoint was selected from the chronic dog study based on decreased body weight changes, hematological and clinical chemistry alterations, and effects on the liver, adrenal gland, and thyroid in both sexes. For short- and intermediate-term inhalation risk assessment, HED selected the POD and endpoint from the subchronic oral (decreased body weight and body

weight gains in females) and chronic dog study (increased liver weight and clinical chemistry changes in both sexes), respectively. Based on both hazard and exposure considerations, HED reduced the required 10X Food Quality Protection Act (FQPA) safety factor (SF) to 1X. Therefore the level of concern (LOC) for inhalation risk assessments is a margin of exposure (MOE) of 100, based on combined interspecies (10X) and intraspecies (10X) uncertainty factors (UFs).

The residue chemistry database is complete for penflufen. The proposed new uses are supported by adequate residue data. The residue of concern in plants and rotational crops is the parent compound only, for both risk assessment and enforcement purposes. Residues in livestock commodities are not expected since quantifiable residues are not likely to occur in any livestock feedstuff. Residues of penflufen were below the limit of quantification (LOQ; 0.01 ppm) in all studies submitted in support of the new uses. Environmentally, penflufen is a moderately mobile chemical that is expected to be persistent in the environment in aerobic and anaerobic conditions. Based on the environmental fate parameters, there is the potential for penflufen to reach drinking water resources. There are no monitoring data available, thus drinking water concentrations were estimated using models. HED has evaluated dietary exposure to penflufen, taking into account all registered and proposed uses and estimated residues in drinking water (D433678, 24 May 2016, J. Cowins). Dietary (food and water) risk estimates for penflufen are not of concern (i.e., less than 100% of the acute and chronic population adjusted doses, aPAD and cPAD). As there are no registered or requested residential uses of penflufen, aggregate exposure and risk estimates are equivalent to dietary exposure, which is not of concern.

No dermal hazard has been identified for penflufen; therefore occupational handler and post-application risks were assessed for the inhalation route of exposure only. All estimated short- and intermediate-term handler inhalation risks greatly exceeded the Agency's level of concern (LOC). Post-application inhalation exposure is expected to be negligible; therefore a quantitative assessment was not required.

Potential areas of environmental justice concerns were considered in this human health risk assessment to the extent possible. For more information, see Section 3.5.

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. Those studies are subject to ethics review, have received that review, and are compliant with applicable ethics requirements.

The most recent risk assessment for penflufen was conducted in 2011 (D387450, 15 November 2011, D. Davis *et al.*), to support the proposed use of the chemical as a new active ingredient on potato, legume vegetables, cereal grains, oilseeds, and alfalfa.

2.0 HED Recommendations

There are no considerations that would preclude registering penflufen as a seed treatment for sugar beets and bulb vegetables (crop group 3-07).

2.1 Data Deficiencies

None.

2.2 Tolerance Considerations

HED has reviewed the petitioned-for tolerances and has recommended appropriate tolerance levels in Table 2.2.2.

The tolerance expression for penflufen should be revised to read as follows:

> "Tolerances are established for residues of the fungicide penflufen, including its metabolites and degradates, in or on the commodities in the table below. Compliance with the tolerance levels for the penflufen is to be determined by measuring only penflufen (*N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide)."

2.2.1 Enforcement Analytical Method

An acceptable analytical method for enforcement was evaluated with the initial penflufen submission. That method includes extraction of residues from matrices into an acetonitrile-based solvent repeatedly, followed by dehydration and the addition of a strong acid and heat to hydrolyze any conjugates. The sample is then neutralized using a strong base, diluted with formic acid in water, and then isotopically labeled with an internal standard. High performance liquid chromatography and triple stage quadrupole mass spectrometry (HPLC/MS/MS) is used to isolate, identify, and quantify residues. For all matrices and analytes, the LOQ, defined as the lowest level of method validation (LLMV), was 0.01 ppm. That same method was used to analyze all samples related to the current petition. Based on concurrent recovers, the method is deemed adequate for tolerance enforcement for the new use commodities.

2.2.2 Recommended Tolerances

Table 2.2.2. Tolerance Summary for Penflufen.

Commodity	Established/Proposed Tolerance (ppm)	HED-Recommended Tolerance (ppm)	Comments (*correct commodity definition*)
Onion, bulb, subgroup 3-07A	0.01	0.01	*Vegetable, bulb, group 3-07* Given that the crops are representative commodities for crop group 3-07, HED recommends setting a crop group tolerance.
Onion, green, subgroup 3-07B	0.015		
Sugar beet, roots	0.01	0.01	*Beet, sugar, roots*
Sugar beet, tops	Not proposed	0.01	*Beet, sugar, tops*

2.2.3 Revisions to Petitioned-For Tolerances

The petitioned-for tolerance level for onion, green [crop subgroup 3-07B] differs from the tolerance level being recommended by HED. The petitioner's proposed level is based on the Organization for Economic Cooperation and Development (OECD) calculation procedure. In addition to this, both representative commodities for crop group 3-07 were submitted for the new uses, which included individual tolerances proposed for crop subgroup 3-07A and 3-07B. Although the petitioner requested separate tolerances based on the aforementioned OECD calculation procedure, HED recommends establishing a tolerance for crop group 3-07 at the LOQ of the enforcement method (0.01 ppm), because maximum residues from crop subgroup 3-07A and subgroup 3-07B representative commodities were within a five-fold difference of each other, and because with residues in the field trials all less than the LOQ, the use of the OECD calculation procedure stipulates that use of the LOQ is appropriate. In addition, by setting the tolerance at 0.01 ppm, EPA will be harmonized with PMRA. Bayer CropScience did not propose a tolerance for residues in the tops of sugar beets. Typically, HED does not recommend setting tolerances on uses classified as non-food; although radiotracer studies indicate that penflufen is not likely to be taken up into the aerial portion of the crops, for harmonization purposes, HED is recommending a tolerance at the LOQ of 0.01 ppm for sugar beet tops.

2.2.4 International Harmonization

The new uses for penflufen are the subject of a joint review with PMRA. The existing tolerances are harmonized. There are no Codex or Mexican MRLs established for residues of penflufen on any crops, including those under review for this petition. The recommended U.S. tolerances for bulb vegetables and sugar beets are being harmonized with the recommended Canadian MRLs; therefore, there are no issues with respect to international harmonization.

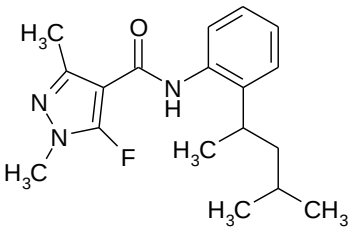
2.3 Label Recommendations

None.

3.0 Introduction

Penflufen is a carboxamide fungicide proposed for use primarily as a seed treatment for protection against certain soilborne, seedborne, and post-emergent diseases of crops. The pesticidal mode of action is as an inhibitor of mitochondrial respiration by inhibiting succinate dehydrogenase, an enzyme in the electron transport system.

3.1 Chemical Identity

Table 3.1. Penflufen Nomenclature	
Chemical Structure	
Empirical Formula	$C_{18}H_{24}FN_3O$
Common Name	Penflufen
Company experimental name	BYF 14182
IUPAC name	2´-[(RS)]-1,3-dimethylbutyl]-5-fluoro-1,3-dimethylpyrazole-4-carboxanilide
CAS Name	N-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1H-pyrazole-4carboxamide
CAS Registry Number	494793-67-8
End-use product/EP	EverGol Energy [264-1122] – Flowable concentrate (3.59% a.i.) EverGol Prime [264-1119] – Flowable concentrate (22.70% a.i.)
Chemical Class	Carboxamide

3.2 Physical/Chemical Characteristics

Technical-grade penflufen is a solid off-white powder at room temperature that is stable at normal and elevated temperatures. The chemical is low in volatility; therefore exposure to penflufen in its vapor phase is not likely. The technical-grade substance has a log K_{OW} of 3.3 indicating a relatively lipophilic nature, but not to a degree that bio-concentration should be of concern. Penflufen has low water solubility and does not dissociate; however, environmentally, penflufen is a moderately mobile chemical that is expected to be persistent in aerobic and anaerobic conditions. Based on the environmental fate parameters, there is the potential for penflufen to reach drinking water resources.

3.3 Pesticide Use Pattern

Two suspension flowable concentrate (SF) formulations are being considered for the new uses of penflufen. Both formulations are to be applied using commercial seed treatment equipment on the day of planting. The proposed use directions are summarized in Table 3.3.

Table 3.3. Summary of Directions for Proposed Uses of Penflufen.			
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/lb seed)[1]**	**Use Directions and Limitations**
Bulb Vegetable Crop Group 3-07			
Commercial Seed Treatment	Flowable Concentrate [264-1119]	0.0025	Apply using slurry or mist-type seed treatment equipment.
Sugar Beets			
Commercial Seed Treatment	Flowable Concentrate [264-1119]	0.000025	Apply using slurry or mist-type seed treatment equipment.

Table 3.3. Summary of Directions for Proposed Uses of Penflufen.			
Applic. Timing, Type, and Equip.	**Formulation [EPA Reg. No.]**	**Applic. Rate (lb ai/lb seed)[1]**	**Use Directions and Limitations**
	[264-1122]		

1. Based on 130,000 seeds per pound for bulb vegetables and 45,454 seeds per pound for sugar beets (from the label).

3.4 Anticipated Exposure Pathways

The use of penflufen on food crops may result in human exposure to residues via food and drinking water (as a result of transport of residues into ground and surface drinking water supplies). There are no residential uses of penflufen, so exposure in residential and non-occupational settings is not likely. In an occupational setting, applicators may be exposed while handling the pesticide prior to application, as well as during application. There is also potential for exposure to planters who are handling treated seeds. The potential for post-application exposures following the planting of penflufen-treated seeds is unlikely because sustained levels of contact with treated seed after it has been planted in the soil or other planting media would not be expected.

3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.eh.doe.gov/oepa/guidance/justice/eo12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are compiled by the USDA under the Continuing Survey of Food Intake by Individuals (CSFII) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific subgroups.

4.0 Hazard Characterization and Dose-Response Assessment

No new toxicology data have been submitted for penflufen in support of the registered/proposed uses. For this assessment, the toxicological endpoints, points of departure (PODs), and uncertainty factors used remain the same as in the previous assessment. Therefore, only a brief

summary of the hazard characterization is provided below. For a detailed penflufen hazard and dose-response characterization, please see the most recent penflufen risk assessment (D387450; D. Davis).

The toxicology database is complete for penflufen and no additional studies are needed. An inhalation toxicity study is not available for penflufen; however, based on a weight of evidence approach, the Hazard Science Policy Council (HASPOC) concluded that an inhalation study is not needed. Additionally, the HASPOC evaluated the need for a comparative thyroid study since thyroid effects were observed in adult animals in the penflufen toxicological database. However, the HASPOC determined that the comparative thyroid study is not required at this time since anticipated exposure to penflufen is low based on the limited use pattern (seed treatment only) and the current PODs selected for risk assessment result in extremely low risk estimates. As a result, the current risk assessments are adequately protective of potential thyroid effects in the young (TXR 0053477). However, the need for the comparative thyroid study will be revisited in in the future if there are changes in the use pattern that would result in significant exposure and/or updated risk estimates.

The liver and thyroid are target organs for penflufen. No evidence of quantitative/qualitative susceptibility was seen in developmental toxicity studies (rats and rabbits). Developmental toxicity was not observed in the rat or rabbit studies, although the studies did not test up to the limit dose. However, new studies are not expected to identify developmental endpoints with points of departure (PODs) lower than those determined in the current studies.
In the reproduction study, decreased pup weight, delayed vaginal patency, and decreased brain, spleen, and thymus weights were seen in the offspring in the presence of limited maternal effects (body weight changes), suggesting qualitative sensitivity. However, concern for the sensitivity is low since the effects are well characterized, there is a clear NOAEL for the effects seen, and the endpoints and PODs selected for risk assessment are protective of the effects. Decreased motor and locomotor activity were observed in both sexes of rats following acute, and in female rats following subchronic, oral exposure; neuropathological lesions were not observed in either study.

The risk assessments conducted for penflufen are based on the most sensitive endpoints in the toxicity database and are protective of all potential effects. Further, highly conservative exposure estimates were incorporated into the dietary (food + water) risk assessment, and there are no residential exposures expected for the existing and proposed uses. Exposure to penflufen will not be underestimated. Based on these considerations, reduction of the 10X FQPA safety factor to 1X is considered appropriate.

For the acute dietary risk assessment, the acute neurotoxicity study was selected with a NOAEL of 50 mg/kg/day based on decreased motor and locomotor activities in females observed at the LOAEL of 100 mg/kg/day. For the chronic dietary risk assessment, the chronic dog study was selected, with a NOAEL of 38 mg/kg/day, based on decreased body weight changes, hematological and clinical chemistry alterations, and effects on the liver, adrenal gland, and thyroid at the LOAEL of 357 mg/kg/day. A dermal risk assessment was not conducted since no dermal hazard was identified. For short-term occupational exposure scenarios involving inhalation exposure, the NOAEL of 55.7 mg/kg/day was selected from the dog oral subchronic

toxicity study. The LOAEL of 532 mg/kg/day was based on decreased body weight changes, clinical chemistry alterations, and liver and adrenal effects. For the intermediate-term occupational exposure scenarios involving inhalation exposure, the NOAEL of 38 mg/kg/day was selected from the chronic dog oral toxicity study discussed above.

For dietary and inhalation risk assessments, the conventional 100x uncertainty factor was applied (10x interspecies factor and 10x intraspecies factor).

4.1 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

Tables 4.1.a and 4.1.b summarize the toxicological doses and endpoints selected for risk assessments. For this assessment, the toxicological endpoints, points of departure (PODs), and uncertainty factors used remain the same as in the previous assessment.

Table 4.1.a Summary of Toxicological Doses and Endpoints for Penflufen for Use in Dietary and Residential (Non-Occupational) Human Health Risk Assessments

Exposure/ Scenario	Point of Departure	Uncertainty/FQPA Safety Factors	RfD, PAD, Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary (All populations, including children and women 13-49 years of age)	NOAEL= 50 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF = 1x	Acute RfD = 0.50 mg/kg/day aPAD =0.5 mg/kg/day	Acute neurotoxicity study in rats (MRID 48023829) LOAEL = 100 mg/kg, based on decreased motor and locomotor activity (39-81% on day of treatment) in females
Chronic Dietary (All Populations)	NOAEL= 38 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF = 1x	Chronic RfD = 0.38 mg/kg/day cPAD = 0.38 mg/kg/day	Chronic toxicity study in dogs (MRID 48023813) LOAEL = 357/425 mg/kg/day, based on decreased terminal body weight and body weight gain (females), increased prothrombin time (males), increased alkaline phosphate activity, decreased cholesterol, increased GGT levels, decreased albumin and albumin/globulin ratio, decreased calcium and phosphorus, increased liver weights, increased incidence of focal hepatocellular brown pigment and hepatocellular hypertrophy, and an increased incidence of thyroid follicular cell hypertrophy in both sexes, and in increased incidence of zona glomerulosa vacuolation of the adrenal gland in females.

Table 4.1.a Summary of Toxicological Doses and Endpoints for Penflufen for Use in Dietary and Residential (Non-Occupational) Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty/FQPA Safety Factors**	**RfD, PAD, Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
* Inhalation Short- Term (1-30 days)	NOAEL= 55.7 mg/kg/day	UF_A= 10 x UF_H=10 x FQPA SF = 1x	Residential LOC for MOE = 100	Subchronic oral toxicity study in dogs (MRID 48023808) LOAEL = 532/568 mg/kg/day, based on decreased body weight/body weight gain (females), clinical chemistry changes, increased liver weights, and increased incidence of hepatocellular hypertrophy in both sexes, and an increased incidence of slight diffuse cortical hypertrophy/hyperplasia in the adrenal in males.
Cancer (oral, dermal, inhalation)	Classification: "Suggestive". Quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to penflufen.			

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. * no residential exposure anticipated for the current seed treatment use.

Table 4.1.b. Summary of Toxicological Doses and Endpoints for Penflufen for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Dermal Short (1-30 days) and Intermediate-Term (1-6 months)	In a 28-day dermal toxicity study in rats, no dermal irritation or systemic effects were observed up to the limit dose of 1000 mg/kg/day. Dermal absorption is minimal (<1%). The quantification of dermal risk is not required since no hazard was identified.			
Inhalation Short-Term (1-30 days)	NOAEL= 55.7 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Subchronic oral toxicity study in dogs (MRID 48023808) LOAEL = 532/568 mg/kg/day, based on decreased body weight/body weight gain (females), clinical chemistry changes (both sexes), increased liver weights (both sexes), increased adrenal weights (males), increased incidence of hepatocellular hypertrophy (both sexes), and an increased incidence of slight diffuse cortical hypertrophy/hyperplasia in the adrenal (males).

Table 4.1.b. Summary of Toxicological Doses and Endpoints for Penflufen for Use in Occupational Human Health Risk Assessments				
Exposure/ Scenario	**Point of Departure**	**Uncertainty Factors**	**Level of Concern for Risk Assessment**	**Study and Toxicological Effects**
Inhalation Intermediate-Term (1-6 months)	NOAEL = 38 mg/kg/day	UF_A=10x UF_H=10x	Occupational LOC for MOE = 100	Chronic toxicity study in dogs (MRID 48023813) LOAEL = 357/425 mg/kg/day, based on decreased body weight/body weight gain (females), increased prothrombin time (males), clinical chemistry changes (both sexes), increased liver weights, and an increase in the incidence of hepatocellular hypertrophy and thyroid follicular cell hypertrophy (both sexes).
Cancer (oral, dermal, inhalation)	Classification: "Suggestive". Quantification of risk using a non-linear approach (i.e. RfD) will adequately account for all chronic toxicity, including carcinogenicity that could result from exposure to penflufen.			

NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. UF_A = extrapolation from animal to human (interspecies). UF_H = potential variation in sensitivity among members of the human population (intraspecies). MOE = margin of exposure. LOC = level of concern

4.2 Safety Factor for Infants and Children (FQPA Safety Factor)

There is potential for dietary exposure to infants and children. The new seed treatment use may result in the potential for exposure through food and drinking water. HED reduced the required 10X FQPA Safety Factor (SF) to 1X based on the following considerations, 1) the toxicity database for penflufen is complete, 2) there is no concern for neurotoxicity or developmental toxicity, 3) although there is evidence of qualitative susceptibility in the rat reproduction study, the offspring effects observed in the study are well characterized and clear NOAELs have been identified in the study for the effects of concern; additionally, the PODs selected for risk assessment are protective of potential offspring effects, and 4) there are no residual uncertainties with respect to dietary and occupational exposure, and there is no potential for exposure from residential sources. The dietary exposure assessment is based on conservative residue levels (that account for parent and metabolites of concern), and processing factors. Furthermore, very conservative, upper-bound assumptions were used to determine exposure through drinking water, such that these exposures have not been underestimated. Actual risk from exposure to penflufen will likely be much lower than HED's risk estimates for the proposed and existing uses. HED's standard toxicological, exposure, and risk assessment approaches are consistent with the requirements of EPA's children's environmental health policy.[1]

4.3 Cancer Classification and Risk Assessment Recommendation

Penflufen is classified as having "suggestive evidence of carcinogenicity. A statistically significant increase in histiocytic sarcomas with a positive trend in male rats only (but in the absence of a dose response and lack of pre-neoplastic lesions) was seen. A marginal increase in brain astrocytomas was also observed in males at the high dose; however, this effect was not dose-related, did not reach statistical significance, and there was no overall trend. In addition,

[1] https://www.epa.gov/children/epas-policy-evaluating-risk-children

there were no pre-neoplastic lesions, such as glial proliferations, which are a good indicator of chemical tumor induction (i.e., there will be changes in the cells prior to transformation to a neoplasm). The ovarian adenomas observed at the high dose also showed no dose response, no pair-wise significance, no decrease in latency, and there were no pre-neoplastic lesions such as hyperplasia of the epithelial cells of the endometrium. Additionally, there was no evidence of carcinogenicity in male or female mice (at doses that were judged to be adequate to assess the carcinogenic potential), no concern for mutagenicity (*in vivo* or *in vitro)* for the parent molecule or the two metabolites, and there were no other lines of evidence (such as structure-activity relationship). Although these three tumors were considered treatment-related, they provided weak evidence of carcinogenicity due to the marginal nature of the tumor responses and the other factors mentioned in this unit. Given the weak evidence indicating any potential for carcinogenicity, EPA has determined that quantification of risk using a non-linear approach (i.e., RfD) will adequately account for all chronic toxicity, including carcinogenicity, which could result from exposure to penflufen. The NOAEL (38 mg/kg/day) used for establishing the chronic RfD is approximately 10-fold lower than the dose (approximately 300 mg/kg/day) that induced a marginal tumor response. The EPA has determined that the chronic population adjusted dose is protective of all long-term effects, including potential carcinogenicity.

5.0 Dietary Exposure and Risk Assessment

5.1 Metabolite/Degradate Residue Profile

For a detailed discussion on plant and livestock metabolism, please see the previous risk assessment (D387450, D. Davis *et al.*, 15 November 2011). The nature of the residue in plants is adequately understood. The metabolites identified in the plant metabolism studies are either found as metabolites in the animal studies, or are intermediaries in the metabolic pathways elucidated in animals; therefore, there are no residues of concern in plant studies, nor are there any unique metabolic pathways in the plant, that are not represented in the rat metabolism study.

The submitted livestock metabolism studies from the previous risk assessment adequately address the requirement to elucidate the nature of the residue in livestock for penflufen. The nature of the residue in livestock commodities is not relevant to the newly proposed uses. There is no reasonable expectation of finite residues in livestock commodities (i.e. in accordance with 40 CFR§180.6(a)(3), there is no reasonable expectation of finite residues); therefore no tolerances are needed.

5.1.1 Summary of Environmental Degradation

Drinking Water Assessment, D428892, I. Abdel-Saheb, 22 February 2016

Penflufen is persistent in aerobic and anaerobic conditions, and is moderately mobile based on the FAO Soil mobility classifications. Penflufen is persistent in soil with half-lives ranging from 115 to 433 days in aerobic soil from two studies conducted in six soils. It degrades very slowly in anaerobic soil with an extrapolated half-life of 886 days. There is no evidence of degradation via hydrolysis, which was studied across environmentally relevant pHs. Penflufen degraded slowly by aerobic aquatic metabolism with half-lives ranging from 267 to 301 days; there is no evidence of degradation in anaerobic aquatic systems. The primary route of degradation is via aqueous photolysis (17 days, corrected environmental half-life of 83.2 days); however photolysis

only plays a significant role in shallow clear waters. Penflufen and its residues of concern (Pen-3HB and AAP) are expected to persist in both the terrestrial and aquatic environments. Pen-3HB is much more mobile than the parent, but the AAP degradate is comparatively immobile. Under aerobic conditions, the compound can be slowly metabolized, but it is stable to anaerobic metabolism. AAP will persist with half-lives ranging from 116-260 days (there is no metabolism data for the Pen-3HB degradate). Penflufen was detected in the submitted terrestrial field dissipation studies above the level of quantitation (LOQ) up to 60cm depth, however the majority of the detections were only reported in the upper soil layers (0-15 cm).

5.1.2 Residues of Concern Summary and Rationale

ROCKS Report, D387299, W. Irwin, 15 June 2011
D395192, D. Davis, 15 November 2011
D387450, D. Davis *et al.*, 15 November 2011

For a detailed discussion for the residues of concern, please see the previous risk assessment and chemistry summary document (D387450, D. Davis *et al.*, 15 November 2011 and D395192, D. Davis, 15 November 2011). Since the structures of the metabolites are similar to the parent, they are assumed to have similar toxicities. The residue of concern for dietary assessment is the parent compound, penflufen.

Table 5.1.2. Metabolites and Degradates to be included in the Risk Assessment and Tolerance Expression.

Matrix		Risk Assessment	Tolerance Expression
Plants	Primary Crop	Penflufen	Penflufen
	Rotational Crop	Penflufen	Penflufen
Livestock	Ruminant	N/A	N/A
	Poultry	N/A	N/A
Drinking Water		Penflufen + penflufen-hydroxybutyl + penflufen-pyrazolyl-AAP	N/A

Penflufen: *N*-[2-(1,3-dimethylbutyl)phenyl]-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
Pen-3HB (penflufen-3-hydroxy-butyl): 5-fluoro-*N*-[2-(3-hydroxy-1,3-dimethylbutyl)phenyl]-1,3-dimethyl-1*H*-pyrazole-4-carboxamide
AAP (penflufen-pyrazolyl-AAP): *N*-(2-acetylphenyl)-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide

5.2 Food Residue Profile

The submitted residue chemistry studies were generally well conducted and are adequate for supporting regulatory conclusions, establishing appropriate tolerance levels for enforcement, and for purposes of risk assessment. Analysis of residues can be accomplished through standard analytical techniques, and residues do not show any trends of dissipation during frozen storage. In biological environments, penflufen undergoes three major pathways of degradation. The proposed new uses of penflufen are seed treatment uses, which can be classified as an early season use profile; resulting in nearly the complete absence (i.e. no quantifiable residues) of parent compound in all residue studies. Radiotracer studies conducted on sugar beets demonstrate that there is no uptake into any of the aerial or root portions of the plant; indicating that penflufen is not taken up by this plant and that there is little likelihood of exposure to penflufen from consuming the edible portions of this commodity. Metabolism studies with goats

and laying hens indicate that residue of concern for both enforcement and risk assessment (penflufen), is unlikely to occur in livestock commodities. The rotational crop data from the previous assessment are adequate and the current plant back interval (PBI) restriction on the current label is appropriate for the new uses.

5.3 Water Residue Profile

Drinking Water Assessment, D428892, I. Abdel-Saheb, 22 February 2016

Estimates of penflufen residues of concern in drinking water were provided by the Environmental Fate and Effects Division (EFED) in a memo titled "Penflufen Drinking Water Assessment for Proposed New Uses on: bulb onion subgroup 3-07A; green onion subgroup 3-07B; and sugar beet seed treatment associated with products EverGol Prime (EPA Reg. No. 264-1119) and EverGol Energy (EPA Reg. No. 264-1122)" (D428982, I. Abdel-Saheb, 22 February 2016). The memorandum notes that the estimated drinking water concentrations (EDWCs) based on the use on potato are derived from the previously registered uses (D387450, D. Davis, *et al*., 15 November 2011). The current drinking water assessment incorporates new models which have been implemented since the previous drinking water assessment was conducted (D386698, R. Baris, 25 August 2011). The previous ground water model, Screening Concentration in GROund Water (SCI-GROW), has been replaced by the Pesticide Root Zone Model for GroundWater (PRZM-GW). As the use patterns for the new crops are lower than the rate that was previously assessed and newer drinking water models were implemented (i.e. Surface Water Concentration Calculator (SWCC) and PRZM-GW), HED has used the higher EDWCs calculated from the use on potato using the PRZM-GW model provided by EFED (D428982, I. Abdel-Saheb, 22 February 2016). The EDWCs for groundwater are greater than those for surface water and are used in the dietary assessment.

Table 5.3. Penflufen Estimated Drinking Water Concentrations for Dietary Risk Assessment (D428982)

Residue Source (Model)	Use Rate, lb a.i./A	Acute EDWC, µg/L	Chronic EDWC, µg/L
Surface Water (SWCC)	0.28	5.09	3.95
Groundwater (PRZM-GW)	0.28	**123**	**84.8**

5.4 Dietary Risk Assessment

Acute and chronic aggregate dietary (food and drinking water) exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16, which uses 2003-2008 food consumption data from the U.S. Department of Agriculture's National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

5.4.1 Description of Residue Data Used in Dietary Assessment

The acute and chronic dietary assessment used tolerance level residues for all commodities included in the assessment.

5.4.2 Percent Crop Treated Used in Dietary Assessment

The acute and chronic dietary risk assessment assumed 100% crop treated for all commodities included in the assessment.

5.4.3 Acute and Chronic Dietary Risk Assessment

A highly conservative acute dietary risk assessment was conducted which used tolerance level residues, assumed 100 percent crop treated (% CT) for all commodities, incorporated a default processing factor for dried commodities and included modeled drinking water estimates. Generally, HED is concerned when risk estimates exceed 100% of the acute and/or chronic population-adjusted dose (aPAD/cPAD). For penflufen, risk estimates are all well below that threshold (Table 5.4.3) and are not of concern. For both acute and chronic dietary assessments, the most highly exposed population subgroup was all infants (<1 year old), at 4% aPAD for the acute assessment, and 1.2% cPAD for the chronic assessment. Due to the conservative nature of the inputs, actual dietary exposure would likely be even lower.

Table 5.4.3. Summary of Acute and Chronic Dietary Exposure (Food and Drinking Water) and Risk Estimates for Penflufen.

Population Subgroup	Acute Dietary (95th Percentile)		Chronic Dietary	
	Dietary Exposure (mg/kg/day)	% aPAD*	Dietary Exposure (mg/kg/day)	% cPAD*
General U.S. Population	0.006790	1.4	0.001837	<1
All Infants (<1 year old)	**0.021114**	**4.2**	**0.004682**	**1.2**
Children 1-2 years old	0.010579	2.1	0.002712	<1
Children 3-5 years old	0.008616	1.7	0.002301	<1
Children 6-12 years old	0.006529	1.3	0.001655	<1
Youth 13-19 years old	0.005678	1.1	0.001355	<1
Adults 20-49 years old	0.006669	1.3	0.001823	<1
Adults 50-99 years old	0.005947	1.2	0.001793	<1
Females 13-49 years old	0.006779	1.4	0.001813	<1

Bold entries are maximum exposure and risk estimates.

6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are currently no existing or proposed residential uses associated with penflufen. Therefore, an assessment for residential handler and post-application exposure is not required.

7.0 Spray Drift Non-Occupational Spray Drift Exposure and Risk Estimates

Spray drift is a potential source of exposure to those nearby pesticide applications. This is particularly the case with aerial application, but, to a lesser extent, spray drift can also be a potential source of exposure from the ground application methods employed for penflufen (seed treatment only). The agency has been working with the Spray Drift Task Force (a task force composed of various registrants which was developed as a result of a Data Call-In issued by

EPA), EPA Regional Offices and State Lead Agencies for pesticide regulation and other parties to develop the best spray drift management practices (see the agency's Spray Drift website for more information). [2] The agency has also developed a policy on how to appropriately consider spray drift as a potential source of exposure in risk assessments for pesticides. The potential for spray drift will be quantitatively evaluated for each pesticide during the *Registration Review* process which ensures that all uses for that pesticide will be considered concurrently. The approach is outlined in the revised (2012) *Standard Operating Procedures for Residential Risk Assessment (SOPs) - Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift.* This document outlines the quantification of indirect non-occupational exposure to drift.

8.0 Aggregate Exposure/Risk Characterization

As there are no registered or requested residential uses of penflufen, aggregate exposure is equivalent to the dietary exposure discussed in Section 5.4. All aggregate risk estimates are below HED's level of concern.

9.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding as to penflufen and any other substances, and penflufen does not appear to produce a toxic metabolite produced by other substances. For the purposes of this action, therefore, EPA has not assumed that penflufen has a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

10.0 Occupational Exposure/Risk Characterization

10.1 Short- and Intermediate-Term Handler Risk

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed use. The quantitative exposure/risk assessment developed for occupational handlers is based on primary and secondary handler scenarios.

Primary Handler (Treating Seed): Potential occupational exposure scenarios from the use of penflufen as a commercial seed treatment include: mixing, loading, and applying liquid formulations to seed; bagging treated seed; and sewing bags with treated seeds. Typically, for large-scale commercial seed treatments, workers perform only those specific individual tasks listed above; however, it is assumed that workers also may perform multiple activities

[2] http://www2.epa.gov/reducing-pesticide-drift

throughout the day. As a result, a "multiple activities" scenario (i.e. where one worker performs all seed treatment tasks such as loading/applying, sewing, bagging, cleaning, calibration, repair, forklift driver, etc.) was also assessed.

Secondary Handler (Planting Treated Seed): Potential occupational exposure scenarios from the use of penflufen as a commercial seed treatment include planting treated seed (secondary handler). Planting treated seed consists of the farmer purchasing bags of treated seed, placing the seed in the hopper and applying seed to fields, considered a secondary handler exposure scenario.

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. The maximum proposed application rates are 0.0025 and 0.000025 lb ai/lb seed for bulb vegetable and sugar beet, respectively, as listed in Table 3.3. The application rates used in the occupational exposure and risk assessment are based on the number of seeds per pound on the proposed product label: bulb vegetable crop group 3-07 (130,000 seeds per pound) and sugar beets (45,454 seeds per pound). Additional standard assumptions such as body weight, amount of seed handled, and unit exposures were used. Each assumption and factor is described in detail in the occupational/residential risk assessment (G. Thornton, D433679; 24 May 2016).

For inhalation exposure, a quantitative assessment was performed for both short and intermediate-term durations, because the toxicological endpoints demonstrate that toxicity increases with increased duration of exposure, and because in commercial seed treatment facilities both short- and intermediate-term exposures are expected. The penflufen product label directs mixers, loaders, applicators and other handlers to wear chemical-resistant gloves.

Combining Exposure/Risk Estimates

As no dermal hazard was identified, combining dermal and inhalation routes of exposure is not applicable.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

The occupational handler inhalation risk estimates (LOC = 100) indicate that there are no risks of concern at or below the label specified level of personal protection (e.g., no respirator). Occupational handler inhalation risk estimates are not of concern with short-term MOEs ranging from 60,000 to 370,000,000 and intermediate-term MOEs ranging from 41,000 to 250,000,000.

Table 10.1.1 Occupational Handler Non-Cancer Short-Term Exposure and Risk Estimates for Penflufen.

Crop or Target	Level of Concern	Inhalation Unit Exposure[1] (mg/lb ai) [Level of PPE]	Maximum Application Rate[2] (lb ai/lb seed)	Amount Of Seed Treated (T) or Planted (P) Per Day[3] (lb seed/day)	Inhalation	
					Dose[4] (mg/kg/day)	MOE[5]
Loader/Applicator						
Bulb Vegetable 3-07	100	0.00034 [Baseline]	0.0025	3,000 (T)	0.000032	1,700,000
Sugar Beet	100	0.00034 [Baseline]	0.000025	3,000 (T)	0.00000032	170,000,000

Table 10.1.1 Occupational Handler Non-Cancer Short-Term Exposure and Risk Estimates for Penflufen.						
Crop or Target	**Level of Concern**	**Inhalation Unit Exposure[1] (mg/lb ai) [Level of PPE]**	**Maximum Application Rate[2] (lb ai/lb seed)**	**Amount Of Seed Treated (T) or Planted (P) Per Day[3] (lb seed/day)**	**Inhalation**	
					Dose[4] (mg/kg/day)	**MOE[5]**
Sewer						
Bulb Vegetable 3-07	100	0.00023 [Baseline]	0.0025	3,000 (T)	0.000022	2,600,000
Sugar Beet	100	0.00023 [Baseline]	0.000025	3,000 (T)	0.00000022	260,000,000
Bagger						
Bulb Vegetable 3-07	100	0.00016 [Baseline]	0.0025	3,000 (T)	0.000015	3,700,000
Sugar Beet	100	0.00016 [Baseline]	0.000025	3,000 (T)	0.00000015	370,000,000
Multiple Activities						
Bulb Vegetable 3-07	100	0.0016 [Baseline]	0.0025	3,000 (T)	0.00015	370,000
Sugar Beet	100	0.0016 [Baseline]	0.000025	3,000 (T)	0.0000015	37,000,000
Planters						
Bulb Vegetable 3-07	100	0.0034 [Baseline]	0.0025	8,800 (P)	0.00094	60,000
Sugar Beet	100	0.0034 [Baseline]	0.000025	3,960 (P)	0.0000042	13,000,000

1 Based on the Science Advisory Council for Exposure Policy 14 (May 2003); Level of mitigation: Baseline, No Respirator.
2 Based on registered or proposed label (Reg. No. 264-1119, 264-1122) using 130,000 bulb vegetable seeds/lb and 45,454 sugar beet seeds/lb.
3 Based on pounds of seed treated per day (sugar beets/small seeded vegetables) from HED Exposure Science Advisory Council Interim Policy 15.1 and pounds of seed planted per acre (sugar beets/pearl onions) from the BEAD memo "Acres Planted Per Day and Seeding Rates of Crops Grown in the United States" (J. Becker, et al; March 2011) and the number of acres planted in a day (ExpoSAC Policy 15).
4 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Amount of Seed Treated/Planted per Day (lb seed/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (55.7 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

Table 10.1.2. Occupational Handler Non-Cancer Intermediate-Term Exposure and Risk Estimates for Penflufen.						
Crop or Target	**Level of Concern**	**Inhalation Unit Exposure[1] (mg/lb ai) [Level of PPE]**	**Maximum Application Rate[2] (lb ai/lb seed)**	**Amount Of Seed Treated (T) or Planted (P) Per Day[3] (lb seed/day)**	**Inhalation**	
					Dose[4] (mg/kg/day)	**MOE[5]**
Loader/Applicator						
Bulb Vegetable 3-07	100	0.00034 [Baseline]	0.0025	3,000 (T)	0.000032	1,200,000
Sugar Beet	100	0.00034 [Baseline]	0.000025	3,000 (T)	0.00000032	120,000,000
Sewer						
Bulb Vegetable 3-07	100	0.00023 [Baseline]	0.0025	3,000 (T)	0.000022	1,800,000
Sugar Beet	100	0.00023 [Baseline]	0.000025	3,000 (T)	0.00000022	180,000,000
Bagger						
Bulb Vegetable 3-07	100	0.00016 [Baseline]	0.0025	3,000 (T)	0.000015	2,500,000
Sugar Beet	100	0.00016 [Baseline]	0.000025	3,000 (T)	0.00000015	250,000,000
Multiple Activities						

Table 10.1.2. Occupational Handler Non-Cancer Intermediate-Term Exposure and Risk Estimates for Penflufen.						
Crop or Target	**Level of Concern**	**Inhalation Unit Exposure[1] (mg/lb ai) [Level of PPE]**	**Maximum Application Rate[2] (lb ai/lb seed)**	**Amount Of Seed Treated (T) or Planted (P) Per Day[3] (lb seed/day)**	**Inhalation**	
					Dose[4] (mg/kg/day)	**MOE[5]**
Bulb Vegetable 3-07	100	0.0016 [Baseline]	0.0025	3,000 (T)	0.00015	250,000
Sugar Beet	100	0.0016 [Baseline]	0.000025	3,000 (T)	0.0000015	25,000,000
Planters						
Bulb Vegetable 3-07	100	0.0034 [Baseline]	0.0025	8,800 (P)	0.00094	41,000
Sugar Beet	100	0.0034 [Baseline]	0.000025	3,960 (P)	0.0000042	9,000,000

1 Based on the Science Advisory Council for Exposure Policy 14 (May 2003); Level of mitigation: Baseline, No Respirator.
2 Based on registered or proposed label (Reg. No. 264-1119, 264-1122) using 130,000 bulb vegetable seeds/lb and 45,454 sugar beet seeds/lb.
3 Based on pounds of seed treated per day (sugar beets/small seeded vegetables) from HED Exposure Science Advisory Council Interim Policy 15.1 and pounds of seed planted per acre (sugar beets/pearl onions) from the BEAD memo "Acres Planted Per Day and Seeding Rates of Crops Grown in the United States" (J. Becker, et al; March 2011) and the number of acres planted in a day (ExpoSAC Policy 15).
4 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/acre or gal) × Amount of Seed Treated/Planted per Day (lb seed/day) ÷ BW (80 kg).
5 Inhalation MOE = Inhalation NOAEL (38 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

10.2 Short- and Intermediate-Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). The potential for dermal and inhalation post-application exposures following the planting of penflufen-treated seeds is unlikely because sustained levels of contact with treated seed after it has been placed in the soil or other planting media would not be expected as no routine cultural practice required for the production of agricultural commodities involves such an activity as defined in the no/low contact criteria in the Worker Protection Standard (WPS). Therefore, no quantitative post-application assessment is required for exposure to treated seeds that have already been planted. The labeling properly states that the WPS allows workers to enter the treated areas without restriction if there is no worker contact with the treated seeds in the soil or planting media.

11.0 References

Cowins, J. 24 May 2016. D433677. *Penflufen. Tolerance Petition for Uses on Sugar Beets and the Bulb Vegetable Crop Group [Crop Group 3-07]. Summary of Analytical Chemistry and Residue Data.*

Cowins, J. 24 May 2016. D433678. *Penflufen. Acute and Chronic Aggregate Dietary (Food and Drinking Water) Exposure and Risk Assessments for the New Use Section 3 Registration Action on Sugar Beets and Bulb Vegetables [Crop Group 3-07].*

Thornton, G. 24 May 2016. D433679. *Penflufen. Occupational and Residential Exposure Assessment for a Proposed Seed Treatment Use on Bulb Vegetable Crop Group 3-07 and Sugar Beets.*

Davis, D., *et al.* 15 November 2016. D387450. *Penflufen. Human Health Risk Assessment to Support New Uses on Potato (Crop Subgroup 1C), Legume Vegetables (Crop Group 6 and Crop Group 7), Cereal Grains (Crop Group 15 and Crop Group 16), Oilseeds (Crop Group 20), and Alfalfa.*

Abdel-Saheb, I. 22 February 2016. D428982. *Penflufen Drinking Water Assessment for Proposed New Uses on: bulb onion subgroup 3-07A; green onion subgroup 3-07B; and sugar beet seed treatment associated with products EverGol Prime (EPA Reg. No. 264-1119) and EverGol Energy (EPA Reg. No. 264-1122)*

Standard Operating Procedure (SOP) Policy 14 for Seed Treatment. May 1, 2003.

Interim Guidance for Policy 15: Amount of Commercial Seed Treated Per Day (Updated March 21, 2013).
Reviewer's Aid to Calculating Occupational Exposures from Activities Related to Agricultural Seed Treatment. November 29, 2012 (Revised).

Acres Planted per Day and Seeding Rates of Crops Grown in the United States. J. Becker. March, 2011.

Attachments:
Appendix A. Toxicology
Appendix B. Metabolism Data
Appendix C. Physical/Chemical Properties
Appendix D. Review of Human Research

Appendix A. Toxicology Profile and Executive Summaries

A.1 Toxicology Data Requirements

The toxicological data requirements (40 CFR 158.340) for food uses for penflufen are in Table A1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table A.1	Test	Technical	
		Required	Satisfied
870.1100	Acute Oral Toxicity	yes	yes
870.1200	Acute Dermal Toxicity	yes	yes
870.1300	Acute Inhalation Toxicity	yes	yes
870.2400	Primary Eye Irritation	yes	yes
870.2500	Primary Dermal Irritation	yes	yes
870.2600	Dermal Sensitization	yes	yes
870.3100	Oral Subchronic (rat and mouse)	yes	yes
870.3150	Oral Subchronic (dog)	yes	yes
870.3200	21/28-Day Dermal (rat)	yes	yes
870.3250	90-Day Dermal	CR	---
870.3465	28-Day Inhalation	CR	No*
870.3700a	Developmental Toxicity (rat)	yes	yes[a]
870.3700b	Developmental Toxicity (rabbit)	yes	yes[a]
870.3800	Reproduction (rat)	yes	yes
870.4100a	Chronic Toxicity (rat)	yes	yes
870.4100b	Chronic Toxicity (dog)	yes	yes
870.4200a	Carcinogenicity (rat)	yes	yes
870.4200b	Carcinogenicity (mouse)	yes	yes
870.4300	Chronic/Carcinogenicity (rat)	yes	yes
870.5100	Mutagenicity—Gene Mutation - bacterial	yes	yes
870.5300	Mutagenicity—Gene Mutation - mammalian	yes	yes
870.5375	Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5395	Mutagenicity—Mammalian Erythrocyte Micronucleus	yes	yes
870.5500	Mutagenicity— Bacterial DNA Damage or Repair Test	no	---
870.5550	Mutagenicity—Unscheduled DNA Synthesis	no	---
870.6100a	Acute Delayed Neurotoxicity. (hen)	no	---
870.6100b	90-Day Neurotoxicity (hen)	no	---
870.6200a	Acute Neurotoxicity Screening Battery (rat)	yes	yes
870.6200b	90 Day Neurotoxicity Screening Battery (rat)	yes	yes
870.6300	Developmental Neurotoxicity (rat)	CR	no
870.7485	General Metabolism (rat)	yes CR	yes yes

Table A.1 Test	Technical	
	Required	Satisfied
870.7600 Dermal Penetration (8-hour), *in vivo* (male rat)		
870.7800 Immunotoxicity (rat and mouse)……	yes	yes
Non-Guideline: Comparative dermal absorption, *in vitro* (rat and human skin)	no	yes
Non-Guideline: 28-day oral toxicity (rat)	no	yes
Non-Guideline: 28-day oral toxicity (mouse)	no	yes
Non-Guideline: 8-hour dermal penetration, in vivo (male rat)	no	yes

[a] ---study acceptable (non-guideline)); study is non-guideline since the highest dose tested was not high enough to produce a dose response, which is a criteria for a guideline study; additional studies are not required since the endpoints selected are protective of any developmental effects that may be seen at higher doses.
*The Hazard Science Policy Council (HASPOC) concluded that an inhalation study is not needed (TXR #0053477)

A.2
Toxicity Profile Tables for Penflufen

Table A.2.1 Acute Toxicity Profile - Test Substance

Guideline No.	Study Type	MRID(s)	Results	Toxicity Category
870.1100	Acute oral – rat	48023749	LD_{50} >2000 mg/kg	III
870.1200	Acute dermal – rat	48023750	LD_{50} >2000 mg/kg	III
870.1300	Acute inhalation - rat	48023801	LC_{50} = 2.022 mg/l	IV
870.2400	Acute eye irritation - rabbit	48023802	Not an irritant	IV
870.2500	Acute dermal irritation – rabbit	48023803	Not an irritant	IV
870.2600	Skin sensitization - guinea pig	48023804	Not a sensitizer	Not applicable

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
NA	28-Day oral toxicity (rat)	48023838 (2004) Acceptable/non-guideline 0, 150, 2000, 7000 ppm (diet) M: 12, 154, 560 mg/kg bw/day F: 13, 169, 648 mg/kg bw/day	NOAEL = 560 mg/kg bw/day (males)/648 mg/kg bw/day (females). LOAEL = not identified; the liver was identified as a major target organ for BYF 14182 (dose-related increase total P-450, BROD, and PROD activities in both sexes, increased cholesterol levels in females, increased liver weight in both sexes, increased incidence of hepatocellular hypertrophy in both sexes). The liver effects are considered adaptive and not adverse.
NA	28-Day oral toxicity (mouse)	48023839 (2005) Acceptable/non-guideline 0, 150, 3500, 7000 ppm (diet) M: 0, 26, 632, 1274 mg/kg bw/day F: 0, 31, 741, 1585 mg/kg bw/day	NOAEL = 1274 mg/kg bw/day (males)/1585 mg/kg bw/day (females). LOAEL = not identified. The liver effects (increased liver weights associated with centrilobular hepatocellular hypertrophy; associated clinical chemistry findings at 7000 ppm) are considered adaptive and not adverse.
NA	28-Day oral toxicity (dog)	48023840 (2005) Acceptable/non-guideline 0, 1300, 6500, 26000 ppm M: 0, 49, 244, and 759 mg/kg bw/day F: 0, 52, 246, and 895 mg/kg bw/day	NOAEL = 759 mg/kg bw/day (males)/895 mg/kg/day (females). LOAEL = not identified. No adverse effects (2 Beagle dogs/sex) administered BYF 14182 *via* the diet (28 days); the liver and thyroid were identified as target organs, as evidenced by increased alkaline phosphatase and GGT activities in both sexes, increased liver weight and increased incidences of hepatocellular hypertrophy, thyroid follicular cell hypertrophy, and decreased follicular diameter in the thyroid in both sexes.
870.3100	90-Day oral toxicity (rat)	48023805(2006) Acceptable/guideline (definitive 90-day rat study, together with the findings of MRID 48023806) 0, 150, 7000, 14000 ppm (diet) M: 0, 9.5, 457 and 949 mg/kg/day F: 0, 11.4, 492 and 1009 mg/kg/day	NOAEL = 949 mg/kg bw/day (males)/1009 mg/kg bw/day (females). LOAEL = not identified. The findings at 14000 ppm included an increase in total cholesterol concentration and gamma-glutamyltransferase activity in both sexes, an increase in the incidence of centrilobular hepatocellular hyper-trophy, which was correlated with higher liver weights and macroscopically enlarged livers in both sexes, an increased incidence of thyroid follicular cell hypertrophy in both sexes, and altered colloid in males. These effects are considered an adaptive response and not adverse.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3100	90-Day oral toxicity (rat)	48023806 (2006) Acceptable/guideline (when considered together with the findings of MRID 48023805) 0, 50, 150, 3500 ppm (diet) M: 0, 3.2, 9.3 and 228 mg/kg bw/day F: 0, 3.7, 11.4 and 260 mg/kg bw/day	NOAEL = 228 mg/kg bw/day (males)/260 mg/kg bw/day (females). LOAEL not identified; increased liver weights and an increased incidence of centrilobular hepatocellular hypertrophy were observed, which were not accompanied by alterations in relevant clinical chemistry parameters or adverse liver lesions. The effects observed are considered adaptive and not adverse over this time frame.
870.3100	90-Day oral toxicity (mouse)	48023807 (2006) Acceptable/guideline 0, 150, 3500, 7000 ppm (diet) M: 0, 26.9, 638, 1238 mg/kg bw/day F: 0, 31.5, 757 and 1600 mg/kg bw/day	NOAEL = 1238 mg/kg bw/day (males)/1600 mg/kg bw/day (females). LOAEL = not identified; liver effects are considered adaptive and not adverse.
870.3150	90-Day oral toxicity (dog)	48023808 (2008) Acceptable/guideline (gavage) M: 0, 5.6, 55.7 and 532 mg/kg bw/day F: 0, 6.1, 63.1 and 568 mg/kg bw/day	NOAEL = 55.7 mg/kg bw/day (males)/63.1 mg/kg bw/day (females), based on the minimal liver effects (increased liver weight and hepatocellular hypertrophy), which were not accompanied by significant alterations in relevant clinical chemistry parameters or adverse liver lesions in both sexes. The effects observed are considered adaptive and not adverse over this time frame. LOAEL = 532 mg/kg bw/day (males)/568 mg/kg bw/day (females), based on decreased body weight/body weight gain in females, increased alkaline phosphatase activity in both sexes, increased GGT activity in both sexes, decreased albumin in males, increased liver weights in both sexes, increased adrenal weights in males, increased incidence of hepatocellular hypertrophy in both sexes, and an increased incidence of slight diffuse cortical hypertrophy/hyperplasia in the adrenal in males.
870.3200	28-Day dermal toxicity (rat)	48023809 (2009) Acceptable/guideline 0, 100, 300, or 1000 mg/kg bw/day	NOAEL = 1000 mg/kg bw/day LOAEL = not identified. Increased lymphocyte debris within the thymic cortex (♂/♀; 7/10 each); lesion characterized by the increased presence of fragmented thymic cortical lymphocytes noted within tingible body macrophages; finding not accompanied by a decrease in the size or weight of the thymus or changes in lymphocyte counts. The significance of the finding at the limit dose is not known.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3465	21/90-Day inhalation toxicity (species)		Not required by HASPOC (TXR#0053477)
870.3700a	Prenatal developmental in (rats)	48023810 (2008) Acceptable/non-guideline 0, 30, 100, or 300 mg/kg bw/day GD 6-20	Maternal toxicity NOAEL = 300 mg/kg bw/day; findings at the 300 mg/kg/day dose level are considered minimal. The dose levels do not appear adequate for assessing the developmental toxicity potential of BYF 14182. Although there was a significant reduction in maternal body weight gain at 300 mg/kg/day, which correlated with a decrease in food consumption, body weights were comparable to those of the control, and the liver changes are considered adaptive and not adverse. Maternal toxicity LOAEL was not identified. Developmental toxicity NOAEL = 300 mg/kg bw/day. At 300 mg/kg/day, the highest dose tested, no adverse effects were observed. However, this dose was a no adverse effect dose level in the range-finding study also. The dose levels are not considered adequate for assessing the developmental toxicity potential of BYF 14182. Developmental toxicity LOAEL was not identified. Little concern that new studies would identify a developmental endpoint with a NOAEL lower than the NOAELs selected for risk assessment.
870.3700b	Prenatal developmental in (rabbit)	48023811(2008) Acceptable/non-guideline 0, 30, 100, or 600 mg/kg bw/day GD 6-28	Maternal NOAEL = 600 mg/kg/day The maternal findings at the 600 mg/kg bw/day dose level are considered minimal. The dose levels do not appear adequate for assessing the developmental toxicity potential of BYF 14182 in the rabbit. Although there was a significant reduction in maternal body weight gain at 600 mg/kg/day, which correlated with a decrease in food consumption, body weights were comparable to those of the control. No other effects were observed. Maternal LOAEL was not identified. Developmental NOAEL = 600 mg/kg bw/day. Developmental toxicity LOAEL was not identified. Little concern that new studies would identify a developmental endpoint with a NOAEL lower than the NOAELs selected for risk assessment.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.3800	Reproduction and fertility effects (rat)	48023812 (2009) acceptable/guideline 0, 200, 1000, or 4000 ppm (diet) M: 0, 12.8, 64.1, 252.2 mg/kg bw/day F: 0, 15, 75.9, 294.5 mg/kg bw/day	**Parental/Systemic** NOAEL = 64 mg/kg bw/day (males)/76 mg/kg bw/day (females) LOAEL = 252.2 mg/kg bw/day (males)/294.5 mg/kg bw/day (females), based on decreased body weight, decreased body weight gain, alterations in food consumption, decreased thymus weight in both genders, and decreased spleen weights in females (both generations). The increased liver weights and hepatocellular hypertrophy are considered adaptive and not adverse. **Reproductive** NOAEL = 73 mg/kg bw/day LOAEL = 291 mg/kg bw/day, based on delayed sexual maturation in females in both generations. **Offspring** NOAEL = 73 mg/kg bw/day LOAEL = 291 mg/kg bw/day, based on a slight decrease in litter size in both generations, decreased pup body weight and pup body-weight gain, delayed vaginal patency in both generations, and decreased brain, spleen, and thymus weights.
870.4100a	Chronic toxicity (rat)	48023815 (2009) Acceptable/guideline 0, 100, 2000 or 7000 ppm (diet) M: 0, 4.0, 79 and 288 mg/kg bw/day F: 0, 5.6, 113 or 399 mg/kg bw/day	NOAEL = 2000 ppm (79/113 mg/kg bw/day) LOAEL = 7000 ppm (288/399 mg/kg bw/day), based on decreased body weight/body weight gain in females, increased liver weight in both sexes, increased incidence of centrilobular to panlobular hepatocellular hypertrophy and centrilobular hepatocellular macrovacuolation in both sexes, increased incidence of hepatocellular brown pigment in females, hepatocellular necrosis, colloid alteration in the thyroid in females, and increased cholesterol in females. These effects are considered mainly adaptive in nature.
870.4100b	Chronic toxicity (dog)	48023813 (2009) Acceptable/guideline 0, 200, 1000, 10000 ppm (diet) M: 0, 6.8, 32.0 and 357 mg/kg bw/day F: 0, 7.7, 37.9 and 425 mg/kg bw/day	NOAEL = 38 mg/kg bw/day. NOAEL is based on the minimal changes in the liver (increased liver weight and hepatocellular hypertrophy, which were not accompanied by relevant changes in clinical chemistry parameters and adverse liver lesions) that are not considered adverse. LOAEL = 357 mg/kg bw/day, based on decreased body weight and body weight gain in females, increased prothrombin time in males, increased alkaline phosphatase activity in both sexes, increased GGT levels in both sexes, increased liver weights in both sexes, increased hepatocellular hypertrophy in both sexes, and an increased incidence of thyroid follicular cell hypertrophy in both sexes.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.4200	Carcinogenicity (rat)	48023815 (2009) Acceptable/guideline 0, 100, 2000 or 7000 ppm (diet) M: 0, 4.0, 79 and 288 mg/kg bw/day F: 0, 5.6, 113 or 399 mg/kg bw/day	See above under 870.4100a. There are three tumor types (brain astrocytomas in males, ovarian tubulostromal neoplasms in females, and histiocytic sarcoma in males). Penflufen was evaluated by the EPA HED Cancer Assessment Review Committee (CARC) on February 16, 2011, and it was concluded that penflufen should be classified Suggestive, quantification not required. All 3 tumor types were considered treatment-related. Dosing was considered adequate based on the presence of tumors.
870.4300	Carcinogenicity (mouse)	48023814 (2009) 0, 100, 1000, 6000 ppm M: 0, 14.3, 146, or 880 mg/kg bw/day F: 0, 18.4, 182, and 1101 mg/kg bw/day	NOAEL = 6000 ppm (880/1101 mg/kg bw/day) LOAEL = LOAEL not identified (included a dose level that exceeded the limit dose in females and one that was close to the limit dose in males. The liver effects and associated effects on the thyroid are considered adaptive and not adverse. **no evidence of carcinogenicity**
Gene Mutation 870.5100	*Ames assay* Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	48023816 (2007) Acceptable/guideline 16 to 5000 µg/plate BYF 14182	Negative with and without metabolic activation
Gene Mutation 870.5100	*Ames assay* Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	48023817 (2009) Acceptable/guideline 3 to 5000 µg/plate BYF 14182	Negative with and without metabolic activation
Gene Mutation 870.5100	*Ames assay* Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	48023818 (2008) Acceptable/guideline 16 to 5000 µg/plate	Negative with and without metabolic activation
Gene Mutation 870.5100	*Ames assay* Salmonella typhimurium TA98, TA100, TA1535, Ta1537, Ta1538	48023819 (2009) Acceptable/guideline 16 to 5000 µg/plate BYF 14182-pyrazolyl-AAP	Negative with and without metabolic activation

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5300	*In vitro* V79/HPRT test – forward mutation (BYF 14182)	48023820 (2007) Acceptable/guideline Experiment 1: without S9: 0, 25, 50, 75, 100, 125, 150 or 175 µg/mL; with S9: 0, 50, 75, 100, 125, 150, 175 or 200 µg/mL Experiment 2: without S9: 0, 12.5, 25, 50, 75, 100 or 125 µg/mL; with S9: 0, 25, 50, 75, 100, 125 or 150 µg/mL	Negative with and without metabolic activation
870.5300	*In vitro* V79/HPRT test – forward mutation (BYF 14182)	48023821 (2009) Acceptable/guideline E1&E2: without S9: 0, 4.5, 9, 18, 27, or 36 µg/mL E1:with S9: 0, 4.7, 9.4, 18.8, 37.5, or 75 µg/mL E2: with S9: 0, 18.8, 37.5, 75, 100, or 125 µg/mL	Negative with and without metabolic activation
870.5300	*In vitro* V79/HPRT test – forward mutation (BYF 14182-3-hydroxy-butyl)	48023822 (2008) Acceptable/guideline 0, 75, 150, 300, 600, 900, or 1200 µg/mL (+/-S9)	Negative with and without metabolic activation
870.5300	*In vitro* V79/HPRT test – forward mutation (BYF 14182-3-pyrazolyl-AAP)	48023823 (2009) Acceptable/guideline 0, 3, 6, 12, 24, 36, 48, or 60 µg/mL (+/-S9)	Negative with and without metabolic activation
870.5375	Chinese Hamster V79 cells – chromosome aberrations (BYF 14182)	48023824 (2007) Acceptable/guideline 4-hour: 0, 10, 20, 40, 70, and 100 µg/mL (-S9) 18-hour: 0, 3, 6, 12, 24, 36 µg/mL (-S9) 4-hour: 0, 15, 30, 60 and 90 µg/mL (+ S9) 4-hour: 0, 40, 70, and 100 µg/mL (-S9) and 0, 60, 75, and 90 µg/mL (+S9) (harvested 30 hours after treatment)	Negative with and without metabolic activation

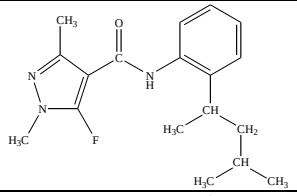
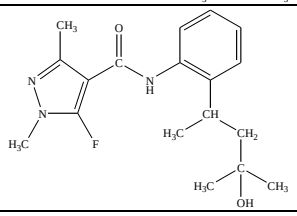
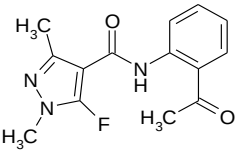
Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.5375	Chinese Hamster V79 cells – chromosome aberrations (BYF 14182)	48023825 (2009) Acceptable/guideline -S9: 0, 9.4, 18.8 and 37.5 g/mL (4-hour treatment) –S9: 0, 4.7, 9.4 and 18.8 µg/mL (18-hour treatment) +S9: 0, 18.8, 37.5 and 75.0 µg/mL (4-hour treatment) +S9: 0, 100, 150 and 300 µg/mL were harvested at 28 hours cytotoxicity determination 4.7-1200 µg/mL (±S9) 2.3-300 µg/mL (±S9).	Negative with and without metabolic activation
870.5375	Chinese Hamster V79 cells – chromosome aberrations (BYF 14182-3-hydroxy-butyl)	48023826 (2008) Acceptable/guideline -S9: 0, 150, 300, 600, 900, and 1200 µg/mL (4-hour treatment), and 0, 75, 150, 300, 450, and 600 µg/mL (18-hour treatment) +S9: 0, 75, 150, 300, 600, and 900 µg/mL (4-hour treatment); harvested 18 hours after treatment. 600, 900, and 1200 µg/mL (-S9) and 300, 600, and 900 µg/mL (+S9); harvested 30 hours after treatment (4-hour treatment).	Negative with and without metabolic activation
870.5375	Chinese Hamster V79 cells – chromosome aberrations (BYF 14182-pyrazolyl-AAP)	48023827 (2009) Acceptable/guideline -S9: 0, 15, 30 and 60 µg/mL (4-hour and 18-hour treatments) +S9: 0, 15, 30 and 60 µg/mL (18-hour harvest after treatment)	Negative with and without metabolic activation
870.5395	Mouse Micronucleus	48023828 (2007) Acceptable/guideline 250, 500, 1000 mg/kg (male)	Negative
870.6200a	Acute neurotoxicity screening battery	48023829 (2009) Acceptable/guideline (gavage) 0, 100, 500, or 2000 mg/kg bw	NOAEL = 50 mg/kg/day LOAEL = 100 mg/kg/day based on decreased motor activity and locomotor activity in females.

Table A.2.2 Subchronic, Chronic and Other Toxicity Profile for Penflufen			
Guideline No.	**Study Type**	**MRID No. (year)/ Classification /Doses**	**Results**
870.6200b	Subchronic neurotoxicity screening battery	48023830 (2009)	NOAEL = 2000 ppm (126/156 mg/kg bw/day LOAEL = 8000 ppm (516/609 mg/kg bw/day based on a slight decrease in motor activity in females, which is consistent with a similar finding of decreased motor activity in females in the acute neurotoxicity study.
870.6300	Developmental neurotoxicity	Not required	
870.7485	Metabolism and pharmacokinetics (species)	48023831 48023832 48023833 48023834 48023835 48023836 (2009)	**Single dose:** elimination pharmacokinetics; rapid absorption & elimination; no apparent effect of increasing dose on absorption or elimination, although differences between sexes in amount in feces/urine. **Metabolism, single dose:** most excreted in feces (males)/urine (females); widely distributed with highest concentration in liver and kidneys; biotransformation characterized as very fast; complex mixture of metabolites. **Metabolic pathway, single dose:** 94-97% excreted; numerous metabolites identified; almost complete absorption **Multiple dosing:** not performed
870.7600	Dermal penetration (rat, male)	48024009 (2009) Acceptable/guideline 1, 50, or 240 g/L for 8 hours (achieved doses ranged from 0.010 to 0.011 mg/cm^2, 0.50 to 0.53 mg/cm^2, and 2.63 to 2.73 mg/cm^2)	maximum % absorbed was 1.442%, 4.152%, and 5.350% for high, mid, and low dose formulations, respectively
OECD 428	*In vitro* dermal absorption (human/rat)	48024011 (2009) Acceptable/non-guideline Doses: 50 g/L, 10 g/L, and 1 g/L	mean total amounts of [^{14}C] considered to be potentially absorbable (*directly absorbed + total remaining at dose site*) at doses of 50 g/L, 10 g/L, and 1 g/L were 4.115%, 5.754%, and 6.516%, respectively, for rat skin and 0.172%, 1.449%, and 1.457%, respectively, for human skin; mean % of the applied dose potentially absorbable was 24-fold, 4-fold, and 4.5-fold greater in the rat skin than in the human skin, respectively.
870.7800	Immunotoxicity	48023837 (2008) Acceptable/guideline 0, 200, 1000 or 7000 ppm M: 0, 17.9, 82.6 or 755.6 mg/kg bw/day F: 0, 20.4, 104.5 or 960.5 mg/kg bw/day	NOAEL = 755.6 mg/kg bw/day for males and 960.5 mg/kg bw/day for females LOAEL = not established.

Appendix B. Metabolism Data

B.1 Structures and Identity of Metabolites of Penflufen

Table B1. Chemical structure, codes and chemical names of penflufen metabolites.

Common Names / Code	IUPAC Name	Chemical Structure
Penflufen BYF 14182	N-[2-(1,3-Dimethylbutyl)phenyl] 5-fluoro-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-3-hydroxy-butyl Pen-3HB BCS-AA10006	5-fluoro-N-[2-(3-hydroxy-1,3-dimethylbutyl)phenyl]-1,3-dimethyl-1H-pyrazole-4-carboxamide	
BYF 14182-pyrazolyl-AAP AE 2300037	*N*-(2-acetylphenyl)-5-fluoro-1,3-dimethyl-1*H*-pyrazole-4-carboxamide	

Appendix C. Physical/Chemical Properties

Table C1. Physical/Chemical Properties of Penflufen		
Parameter	**Value**	**Reference**
Molecular Weight	317.41 g/mol	MRID No. 48023535
pH	6.7 (1% suspension in distilled water @ 22°C)	MRID No. 48023525
Water solubility (20°C)	@ pH 4 = 11.0 mg/L @ pH 7 = 10.9 mg/L @ pH 9 = 11.2 mg/L	MRID No. 48023535
Solvent solubility (20°C)	Solvent g/L methanol 126 n-heptane 1.6 toluene 62 dichloromethane >250 acetone 139 ethylacetate 96 dimethyl sulfoxide 162	MRID No. 48023536
Vapor pressure (25°C)	9.0×10^{-9} torr	MRID No. 48023537
Dissociation constant, pKa	No dissociation constant (pKa) was found in aqueous solution of penflufen in the range of 1<pH<12. The molecule has no structural moieties which are prone to dissociate.	MRID No. 48023532
Henry's law constant	1.04×10^{-10} atm·m^3/mol	MRID No. 48023539
Octanol/water partition coefficient, log K_{OW} (25°C)	@pH 7 = 3.3	MRID No. 48023534
Hydrolysis $t_{1/2}$ at 50°C	Stable	MRID No. 48023547
Aqueous photolysis $t_{1/2}$ at 25°C	83.2 days	MRID No. 48023548
Aerobic soil metabolism $t_{1/2}$ at 25°C (combined radio-label half-life)	249 days (silt loam) 433 days (sandy loam)*	MRID No. 48023553
Aerobic soil metabolism $t_{1/2}$ at 20ºC	117 days (silt loam) 165 days (sandy loam)* 243 days (loam)* 129 (loam)*	MRID No. 48023552,
	AAP (degradate) 257 days (sandy loam)* 116 days (silt loam) 231 days (loam)* 128 days (clay loam)*	MRID No. 48023554
Anaerobic Soil Metabolism $t_{½}$ at 20°C	866 days*	MRID No. 48023555
Aerobic aquatic metabolism $t_{1/2}$ at 20°C (sandy loam:sediment system, 2 radio-labels)	301 days* 267 days	MRID No. 48023556
Anaerobic aquatic metabolism $t_{1/2}$ at 20°C (combined labels)	Stable	MRID No. 48023557

* Extrapolated beyond the study duration.

Appendix D. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from the Agricultural Handler Exposure Task Force (AHETF) database; and ExpoSAC Policies 14, 15, and 15.1 (SOPs for Seed Treatment); are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website. [3]

[3] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure